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10/552,287	01/04/2007	Anthony Futerman	30227	6293

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,287	FUTERMAN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *139-156* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *123-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/27/07 and 5/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

Continuation of Disposition of Claims: Claims pending in the application are 123-124, 126-129, 131, and 133-159 (renumbered as claims 123-156).

DETAILED ACTION

Status of the Application

[1] Claims 123-124, 126-129, 131, 133-159 are pending in the application.

[2] Applicant's amendment to the claims, filed on 6/2/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. Claims 123 and 131 have been amended relative to claim set filed on 10/4/05.

[3] The numbering of claims as set forth in the claim listing filed on 6/2/08 is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 126-129 have been renumbered 125-128, misnumbered claim 131 has been renumbered 129, and misnumbered claims 133-159 have been renumbered 130-156. For applicant's convenience, a copy of the renumbered claim listing is attached to this Office action as Appendix A. Receipt of an information disclosure statement, filed on 5/7/08, is acknowledged.

Election/Restriction

[5] Applicant's election of Group I, renumbered claims 123-138 and election of species a) glucocerebrosidase of Table 4 and SEQ ID NO:1 and species m) glycosylation residue 1, Asn19 in the reply filed on 6/2/08 is acknowledged. Because

applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

[6] Claims 139-156 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 6/2/08.

[7] Claims 130-133 have been examined only to the extent the claims read on the elected species of a) glucocerebrosidase of Table 4 and SEQ ID NO:1.

Claim to Priority

[8] According to the bibliographic data sheet, the instant application is a national stage filing under 35 U.S.C. 371 of PCT/IL04/00335, filed on 4/18/04, which claims domestic priority under 35 U.S.C. 119(e) to US provisional application 60/463,049, filed on 4/16/03.

[9] Claims 1-8 of application PCT/IL04/00335 appear to provide descriptive support for claims 123-128 herein; claims 57-75 of application PCT/IL04/00335 appear to provide descriptive support for claims 129-137 herein; and claim 87 of application PCT/IL04/00335 appears to provide descriptive support for claim 141 herein.

[10] Regarding priority to the provisional application, it is noted that 4/16/04 fell on a Friday, which does not appear to have been a Federal holiday, and thus this application was not filed within twelve months from the filing date of the provisional application, and there is no indication of an intermediate nonprovisional application that is directly

claiming the benefit of the provisional application and filed within 12 months of the filing date of the provisional application.

Note: If the day that is 12 months after the filing date of the provisional application falls on a Saturday, Sunday, or Federal holiday within the District of Columbia, the nonprovisional application claiming the benefit of the provisional application may be filed on the next succeeding business day.

Applicant is required to delete the reference to the prior-filed provisional application from the first sentence(s) of the specification or the application data sheet, depending on where the reference was originally submitted, unless applicant can establish that this application, or an intermediate nonprovisional application, was filed within 12 months of the filing date of the provisional application.

[11] The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/463,049, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. See claim 123, reciting "a partially glycolated crystallized glucocerebrosidase molecule"; see claim 125, which recites "about" with respect to the lengths of a, b, and c; see claims 128, which recites

"SEQ ID NO:1", wherein the sequence of SEQ ID NO:1 does not appear to be disclosed in the provisional application; see claim 129, the limitations of (i), (ii), and (iii); see claims 130-132, pointing to particular glycosylation residues and reciting "SEQ ID NO:1"; and see limitations of claims 127 and 133-138.

[12] Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Israel application 156273, filed on 6/2/03. The certified copy has been filed in the instant application on 10/4/05.

While the foreign priority document appears to provide descriptive support for the limitations of claims 123-128, the examiner can find no support for the limitations of claims 129-138 in the foreign priority document.

[13] Accordingly, claims 123-128 are accorded a priority date of 6/2/03, while claims 129-138 are accorded a priority date of 4/18/04.

Information Disclosure Statement

[14] With the exception of references 4 and 20 of the information disclosure statement (IDS) filed on 6/27/07, all references cited in the IDSs filed on 6/27/07 and 5/7/08 have been considered by the examiner. A copy of Forms PTO/SB/08 is attached to the instant Office action.

Reference 4 of the 6/27/07 IDS has been lined through as the incorrect page numbers are listed in the IDS citation and the reference has been made of record on the attached PTO-892.

Reference 20 of the 6/27/07 IDS has been lined through because the reference is in a foreign language and there is no "concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language" in accordance with 37 CFR 1.98(a)(3)(i).

[15] If the examiner has inadvertently overlooked an IDS in the application file, applicant is kindly requested to alert the examiner to this oversight in the response to this Office action.

Oath/Declaration

[16] The oath or declaration filed on 1/4/07 is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: It does not identify the citizenship of each inventor.

Specification/Informalities

[17] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Partially Deglycosylated Glucocerebrosidase Polypeptide and Crystal Thereof---.

[18] As noted in the prior Office action, in order to perfect compliance with the rules for a sequence listing, applicant is required to submit a formal amendment to the

specification in accordance with 37 CFR 1.121, directing entry of the substitute sequence listing paper copy filed on 1/4/07 into the application.

[19] The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. See, *e.g.,* p. 3, lines 8-9. Applicant is requested to review the instant specification and delete all embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

[20] The transmittal letter and specification filed on 10/4/05 indicate the filing of a CD-ROM. The following objections apply to the CD-ROM submission. Applicant's attention is directed to MPEP 608.05. Applicant is requested to review and fully comply with the requirements for a CD-ROM submission.

[a] This application is objected to under 37 CFR 1.52(e)(4) because it does not contain a statement in the transmittal letter that the two compact discs are identical. Correction is required.

[b] This application contains compact disc(s) as part of the originally filed subject matter, but does not contain an incorporation by reference statement for the compact discs. See 37 CFR 1.77(b)(4). Applicant(s) are required to insert in the specification an incorporation-by-reference of the material on the compact disc(s).

Claim Objections

[21] Claim 123 is objected to in the recitation of "glycoylated", which appears to be a misspelling of "glycosylated".

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[22] Claims 124, 127, and 129-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Because resolution of x-ray diffraction is inversely related to angstrom numerical value, claim 124 is indefinite in the recitation of "resolution of 2.9 angstroms or higher" as it is unclear as to whether the term "higher" refers to resolution or angstroms. It is suggested that applicant clarify the meaning of the noted phrase.

[b] Claim 127 is indefinite in the recitation of "displaying normal enzymatic activity" because: 1) enzymatic activity is not recognized as being displayed; 2) it is unclear as to whether the noted phrase is intended to refer to a quantitative or qualitative measure of enzymatic activity; and 3) if a quantitative measure of enzymatic activity is intended, it is noted that "normal" is a relative term and it is unclear as to what applicant intends as being a "normal" enzymatic activity.

[c] Claim 129 (claims 130-138 dependent therefrom) are confusing in the recitation of "glycosylation residues 2, 3, and 4 of said amino acid sequence". Typically, the art recognizes designation of a residue number to refer to the amino acid position within an amino acid sequence with the N-terminal amino acid being residue 1. However, based on dependent claims 130-132, which indicate that glycosylation residues 2, 3, and 4 are intended as encompassing Asn59, Asn146, and Asn270, respectively, of SEQ ID NO:1,

the designation of residues 2, 3, and 4 is not intended to refer to amino acid position numbering within an amino acid sequence. It is suggested that applicant clarify the meaning of the noted phrase.

[d] Claims 130-132 are indefinite in the recitation of "represented by" as it is unclear as to the intended meaning of the phrase. In this case, the noted phrase has at least two meanings: 1) glycosylation residues 2, 3, and 4 *are* Asn59, Asn146, and Asn270 of SEQ ID NO:1, respectively, or Asn59, Asn146, and Asn270 of SEQ ID NO:1 are intended only as representative, *i.e.,* exemplary, glycosylation residues 2, 3, and 4. It is suggested that applicant clarify the meaning of the noted phrase.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[23] Claim(s) 123-138 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

CLAIM INTERPRETATION: According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what

the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

Claims 123-128 are drawn to a genus of crystals of a partially glycosylated glucocerebrosidase polypeptide, characterized by an x-ray diffraction capacity enabling generation of a set of structural coordinates comprising a set of structural coordinates of Table 4. In view of the use of the recitation of "a set of structural coordinates of Table 4" (rather than, *e.g.,* "the structural coordinates of Table 4"), the examiner has interpreted this phrase as meaning any two or more x, y, and/or z coordinates of Table 4. Thus, with the exception of claim 128, the structure of the glucocerebrosidase polypeptide is undefined and unlimited. Also, with the exception of claims 125-126, the characteristic(s) of the crystal are undefined and unlimited.

Claims 129-138 are drawn to a preparation of a genus of purified glucocerebrosidases having an amino acid sequence at least 95% homologous to an amino acid sequence of SEQ ID NO:1; being glycosylated at Asn19; being unglycosylated at one or more of glycosylation residues 2, 3, and 4 and being able to form pure glucocerebrosidase crystals having an x-ray diffraction capacity enabling generation of a set of structural coordinates comprising a set of structural coordinates of Table 4. In view of a broad, but reasonable interpretation, the examiner has interpreted these claims as encompassing both crystalline and non-crystalline polypeptides. In view of the use of the recitation of "an amino acid sequence of SEQ ID NO:1" (rather than,

e.g., "the amino acid sequence of SEQ ID NO:1"), the examiner has interpreted this phrase as meaning any two or more contiguous amino acids of SEQ ID NO:1. Also, as noted above, in view of the use of the recitation of "a set of structural coordinates of Table 4" (rather than, *e.g.*, "the structural coordinates of Table 4"), the examiner has interpreted this phrase as meaning any two or more x, y, and/or z coordinates of Table 4. Thus, the structure of the glucocerebrosidase polypeptide is undefined and unlimited.

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention".

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163

states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification discloses only a single representative species of a non-crystalline glucocerebrosidase polypeptide that is able to form pure crystals for generation of the structural coordinates of Table 4, *i.e.,* non-crystalline, deglycosylated SEQ ID NO:1, prepared according to the method as disclosed at p. 80, lines 5-16. Also, the specification discloses only a single representative species of crystals of glucocerebrosidase, *i.e.,* a crystal of deglycosylated SEQ ID NO:1 as prepared according to the method as disclosed at p. 80, lines 5-16, having the space group $C222_1$ and the unit cell dimensions a=107.7 Á b=285.2 Á, c=91.8 Á that diffracts x-rays to a resolution of 2.0 Á. Other than these disclosed species, the specification fails to describe any additional representative species of the claimed polypeptide or crystal. According to MPEP 2163.II.A.2.(a).ii), "For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Because the art of protein crystallization is highly unpredictable (see below discussion regarding the state of the art of protein crystallization), the single representative species as noted above fail to describe all polypeptides and crystals as encompassed by each respective genus. The claimed polypeptide and crystal encompass widely variant species and given the lack of

description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[24] Claims 123-138 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) non-crystalline, deglycosylated SEQ ID NO:1, prepared according to the method as disclosed at p. 80, lines 5-16; and

2) a crystal of deglycosylated SEQ ID NO:1 as prepared according to the method as disclosed at p. 80, lines 5-16, having the space group $C222_1$ and the unit cell dimensions a=107.7 Å b=285.2 Å, c=91.8 Å that diffracts x-rays to a resolution of 2.0 Å, does not reasonably enable all polypeptides and crystals as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction

provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims...claims are to be given their broadest reasonable interpretation that is consistent with the specification."

CLAIM INTERPRETATION: As noted above, claims 123-128 are drawn to a genus of crystals of a partially glycosylated glucocerebrosidase polypeptide, characterized by an x-ray diffraction capacity enabling generation of a set of structural coordinates comprising a set of structural coordinates of Table 4. In view of the use of the recitation of "a set of structural coordinates of Table 4" (rather than, *e.g.*, "the structural coordinates of Table 4"), the examiner has interpreted this phrase as meaning any two or more x, y, and/or z coordinates of Table 4. Thus, with the exception of claim 128, the structure of the glucocerebrosidase polypeptide is undefined and unlimited. Also, with the exception of claims 125-126, the characteristic(s) of the crystal are undefined and unlimited.

As further noted above, claims 129-138 are drawn to a preparation of a genus of purified glucocerebrosidases having an amino acid sequence at least 95% homologous to an amino acid sequence of SEQ ID NO:1; being glycosylated at Asn19; being unglycosylated at one or more of glycosylation residues 2, 3, and 4 and being able to form pure glucocerebrosidase crystals having an x-ray diffraction capacity enabling generation of a set of structural coordinates comprising a set of structural coordinates of Table 4. In view of a broad, but reasonable interpretation, the examiner has interpreted these claims as encompassing both crystalline and non-crystalline polypeptides. In view of the use of the recitation of "an amino acid sequence of SEQ ID NO:1" (rather than, *e.g.,* "the amino acid sequence of SEQ ID NO:1"), the examiner has interpreted this phrase as meaning any two or more contiguous amino acids of SEQ ID NO:1. Also, as noted above, in view of the use of the recitation of "a set of structural coordinates of Table 4" (rather than, *e.g.,* "the structural coordinates of Table 4"), the examiner has interpreted this phrase as meaning any two or more x, y, and/or z coordinates of Table 4. Thus, the structure of the glucocerebrosidase polypeptide is undefined and unlimited.

The broad scope of claimed crystals and polypeptides is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to being enabling for non-crystalline, deglycosylated SEQ ID NO:1, prepared according to the method as disclosed at p. 80, lines 5-16; and a crystal of deglycosylated SEQ ID NO:1 as prepared according to the method as disclosed at p. 80, lines 5-16, having the space group $C222_1$ and the unit cell dimensions a=107.7 Á b=285.2 Á, c=91.8 Á that diffracts x-rays to a resolution of 2.0 Á.

The nature of the invention: The invention is related to diffraction-quality crystals and polypeptides able to crystallize to achieve a diffraction-quality crystal for identifying potential therapeutics (specification at p. 4, beginning at line 27). At the time of the invention, methods of protein crystallization were well-known in the art. However, such methods are largely empirical and the ability to crystallize a given protein was, at the very least, challenging and unpredictable to a skilled artisan as even minor alterations in the amino acid sequence of the polypeptide, ligand, and/or conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: According to MPEP 2164.03, "what is known in the art provides evidence as to the question of predictability…in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims".

At the time of the invention, the state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "The first prerequisite for solving the three-dimensional structure of a protein by x-ray crystallography is a well-ordered crystal that will diffract x-rays strongly…[w]ell-ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular

surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1999) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Also, Wiencek (*Ann Rev Biomed Eng* 1:505-534, 1999) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom).

Additionally, Buts et al. (*Acta Cryst* D61:1149-1159, 2005) teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution." Specifically, the reference of Buts *et* al. teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G

adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99% identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3).

Skarzynski et al. (Acta Cryst D62:102-107, 2006) teaches "crystals of complexes obtained by compound soaking may become damaged, change their diffraction properties or even change the space group during the soaking experiment!" (p. 103, right column, middle). Skarzynski et al. further teaches that binding of potent compounds during soaking often causes complete or partial disruption of the crystal lattice, poorly soluble compounds may interfere with the diffraction pattern of the protein crystal sample, and very often no binding is observed for active compounds, despite their potency under biochemical or biological assay conditions" (p. 104, left column, middle). The teachings of Skarzynski et al. are supported by applicant's specification, which teaches "Attempts to soak the GDP-4-keto, 6-deoxy mannose substrate or GDP into the crystals failed" (p. 15, top).

Even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. *Cell. Mol. Life Sci.* 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see also Weber, *Methods in Enzymology*, 1997, Vol. 276, pp. 13-22). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Drenth, *supra,* Cudney, *Rigaku Journal*, 1999, Vol. 16, No. 1, pp. 1-7, and Saphire, *Nature,* 2008, Vol. 454, p. x).

McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990) teaches (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out

trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual."

It appears that applicant acknowledges such unpredictability by disclosing that approaches to determine a 3D structure for CEREZYME (SEQ ID NO:1) "have essentially failed" (p. 5, lines 7-12).

Thus, in view of these teachings, a skilled artisan would recognize there is a high level of unpredictability in making a diffraction-quality protein crystal or a polypeptides suitable for such.

The amount of direction provided by the inventor; The existence of working examples: According to MPEP 2164.03, "if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling".

The specification discloses only a single working example of a non-crystalline glucocerebrosidase polypeptide that is able to form pure crystals for generation of the structural coordinates of Table 4, *i.e.,* non-crystalline, deglycosylated SEQ ID NO:1, prepared according to the method as disclosed at p. 80, lines 5-16. Also, the specification discloses only a single working example of a crystal of glucocerebrosidase, *i.e.*, a crystal of deglycosylated SEQ ID NO:1 as prepared according to the method as disclosed at p. 80, lines 5-16, having the space group $C222_1$ and the unit cell dimensions a=107.7 Å b=285.2 Å, c=91.8 Å that diffracts x-rays to a resolution of 2.0 Å. However, these working examples fail to provide the necessary guidance for making the entire scope of proteins and crystals as broadly encompassed by the claims. The specification fails to provide guidance regarding alterations in, *e.g.*, the amino acid sequence, method of polypeptide preparation, optional ligand, and crystallization conditions, *e.g.*, protein concentration, buffer (components, concentrations, and pH), and temperature, with an expectation of obtaining a diffraction-quality crystal.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention, it was not routine in the art to screen all polypeptides for those that will yield diffraction-quality crystals.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would

be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[25] Claim(s) 129-137 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dvir et al. (*EMBO Reports* 4:704-709, 2003; "Dvir"). As noted above, claims 129-137 have been accorded a priority date of 4/18/04. The examiner's broadest reasonable interpretation of the claims is discussed *supra*.

Dvir teaches the amino acid sequence of CEREZYME® (p. 707, Figure 4A), which appears to be 100% identical to SEQ ID NO:1 herein. Dvir teaches a preparation of deglycosylated CEREZYME® that has been treated with N-glycosidase F and stored in a buffered solution, (p. 708, column 1, bottom), which is considered to be a pharmaceutical composition. Dvir teaches the N-glycosidase F-treated CEREZYME® has 7-14 sugar residues removed (p. 708, column 1, bottom) and maintains glycosylation at Asn19, which is required for catalytic activity (p. 704, column 2, bottom). Dvir teaches crystallization of the N-glycosidase F-treated CEREZYME® to generate structural coordinates (p. 708, column 2). This anticipates claims 129-137 as written.

EXAMINER CLARIFICATION: Regarding a rejection under 35 U.S.C. 102/103, see MPEP 2112.III, which states, "Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection".

In this case, the reference of Dvir fails to expressly teach the following limitations: 1) N-glycosidase F-treated CEREZYME® is deglycosylated at glycosylation residues 2,

3, and/or 4 (claims 129-132); 2) N-glycosidase F-treated CEREZYME® has the same capacity for hydrolysis as untreated CEREZYME® (claim 133); 3) N-glycosidase F-treated CEREZYME® has an exposed mannose residue (claim 134); and 4) N-glycosidase F-treated CEREZYME® is capable of being internalized by a phagocyte (claim 135). However, these characteristics would appear to be present in N-glycosidase F treated CEREZYME® because according to the specification, N-glycosidase F-treated CEREZYME® results in deglycosylation of at least one of Asn59, Asn146 and Asn270 (pp. 92-93) and maintains its original enzymatic activity (p. 93, middle) and macrophage uptake ability (p. 95, top) due to exposed mannose residues (p. 96, middle).

Regarding claims 136-137, it is noted that the limitation of "for treating a disease..." in claim 136 has been interpreted as an intended use limitation and has been accorded no patentable weight in accordance with MPEP 2111.02.II.

Claim Rejections - 35 USC § 103

[26] The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 138 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dvir (*supra*).

The relevant teachings of Dvir are described above. Dvir further teaches preparation of crystals and cryoprotection of crystals (p. 708 under *METHODS*). Dvir does not expressly teach an article of manufacture comprising packaging material and N-glycosidase F-treated CEREZYME®.

At the time of the invention, it would have been obvious to store the cryoprotected crystal of N-glycosidase F-treated CEREZYME® in a storage container (a packaging material) and store the container in a freezer (an article of manufacture) for storage. One would have been motivated to do this in order to preserve the crystal. One would have had a reasonable expectation to store the cryoprotected crystal of N-glycosidase F-treated CEREZYME® in a storage container and store the container in a freezer because of the teachings of Dvir. Therefore, the article of manufacture of claim 138 would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[27] Status of the claims:

- Pending claims 123-124, 126-129, 131, and 133-159 have been renumbered as claims 123-156.
- Claims 139-156 are withdrawn from consideration.
- Claims 123-138 are rejected.

- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656